## REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims presented herein.

## I. Status of the Claims

In this Amendment A, claims 1, 2, 4, 6, 8, and 10-14 have been amended in order to more particularly claim certain embodiments of the present application. Additionally, claims 5, 7 and 9 have been cancelled.

Accordingly, upon entry of this Amendment A, claims 1-4, 6, 8 and 10-26 will be pending. Claims 8, 12 and 21-26 remain withdrawn from consideration at this time, for being directed to non-elected subject matter. As such, claims 1-4, 6, 10, 11 and 13-20 are currently under examination.

Claim 1 has been amended to more particularly define the substituents of Formula I and Formula II. In addition to the language of the claim as originally presented, support for the amendment to the substituents can be found, for example, in the application as follows:

Formula I:

- $A_1$ and $B_1$: paragraph [0028] of the published application (US 2008/0317675 A1) and claim 4 as originally filed; and,
- $D_1$: paragraph [0028] of the published application and claim 5 as originally filed.

Formula II:

- $A_2$ and $A_3$: paragraph [0039] of the published application and claim 2 as originally filed; and,
- $B_3$ and $D_2$: paragraph [0039] of the published application.

Claim 2 has been amended to require, with regard to Formula I, $R_1$ to be hydrogen or methyl. Support for this amendment can be found, for example, in paragraph [0039] of the published application.

Claim 4 has been amended to ensure the definitions of the substituents of Formula I and Formula II therein are consistent with claim 1. Support for these amendment can be found, for example, in paragraphs [0028] and [0039] of the published application.

Claim 6 has been amended to require $A_1$ and $B_1$ to be $-CONHR_3$. Support for this amendment can be found, for example, in paragraph [0028] of the published application.

Withdrawn claim 8 has been amended to require that each of $R_1$ and $R_3$ of $A_1$ and $B_1$ is independently selected from methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl or dihydroxypropyl. Support for this amendment can be found, for example, in paragraph [0028] of the published application.

Claim 10 has been amended in order to be consistent with claim 1, as amended. Accordingly, support may be found, for example, in paragraph [0028] of the published application.

Claim 11 has been amended to require $A_1$ and $B_1$ to be $-CONHR_3$. Support for this amendment can be found, for example, in paragraph [0028] of the published application.

Withdrawn claim 12 has been amended to require that each of $R_1$ and $R_3$ of $A_1$ and $B_1$ is independently selected from methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl or dihydroxypropyl. Support for this amendment can be found, for example, in paragraph [0028] of the published application.

Claim 13 has been amended to require $R_1$ to be hydrogen. Support for this amendment can be found, for example, in paragraph [0028] of the published application.

Finally, claim 14 has been amended to require $B_3$ and $D_2$ to be -CONHR. Support for this amendment can be found, for example, in paragraph [0039] of the published application.

## II. The Pending Claims Are Not Obvious

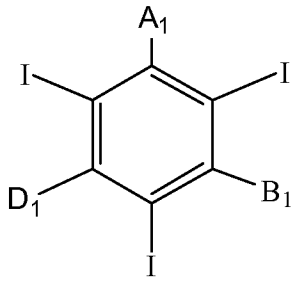
Applicants request reconsideration of the rejection of claims 1-4, 6, 8, 10, 11 and 13-20

as unpatentable under 35 U.S.C. § 103(a) over Felder (US 5,695,742) in view of Sovak (US 5,698,739).

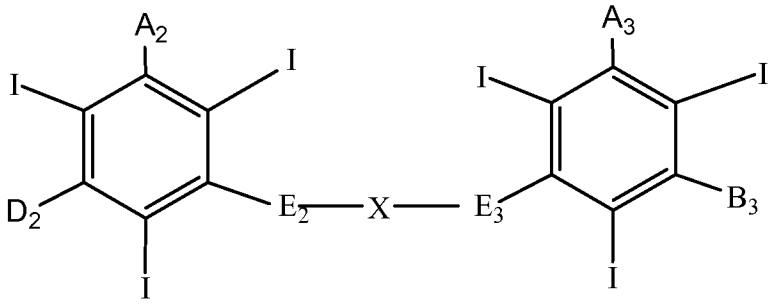
**A. The Claimed Subject Matter and Felder and Sovak**

**(i) The Claimed Subject Matter**

Claim 1, from which all other rejected claims depend, is directed to an injectable radiological composition for x-ray visualization during radiological examinations. The composition comprises a pharmaceutically acceptable vehicle and a mixture of at least one monomer (corresponding to Formula I) and at least one dimer (corresponding to Formula II):




Formula (I)




Formula (II)

wherein, with regard to Formula I:

$A_1$ and $B_1$ are $-CON(R_3)R_1$;

$D_1$ is $-N(R)C(O)R_2$;

each R and $R_2$ is independently H, or a linear or branched ($C_1$-$C_8$) alkyl residue, optionally substituted by one or more hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

each $R_1$ is independently (i) hydrogen, or (ii) a linear or branched ($C_1$-$C_8$) alkyl residue, optionally substituted with one or more hydroxy, alkoxy,

hydroxyalkoxy groups or combinations thereof;

each $R_3$ is independently linear or branched ($C_1$-$C_8$) alkyl residue, optionally substituted with one or more hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

and wherein with regard to Formula II:

$A_2$ and $A_3$ are -$CONH_2$;

$B_3$ and $D_2$ are -$CON(R)R_1$;

$E_2$ and $E_3$ are independently selected from the group consisting of -CON(R)-,

-N(R)C(O)- and -$N(COR_2)$-;

each R is independently H, or a linear or branched ($C_1$-$C_8$) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof;

each $R_1$ is independently (i) hydrogen, (ii) a linear or branched ($C_1$-$C_8$) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof, or (iii) the residue of a carbohydrate;

or R and $R_1$ are each members of a ($C_3$-$C_7$) cyclic residue further comprising the nitrogen atom to which each of R and $R_1$ is bonded, said cyclic residue being optionally interrupted by -O-, -S- or -$NR_4$-, and/or optionally substituted by one or more hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

each $R_2$ is independently a linear or branched ($C_1$-$C_8$) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof;

each $R_4$ is independently hydrogen or a linear branched ($C_1$-$C_8$) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof; and

X is a bond or a linear or branched ($C_1$-$C_8$) alkylene chain which is optionally substituted by up to six hydroxyl groups, said alkylene chain being optionally interrupted by -O-, -S-, -$NR_4$- or -N(R)C(O)- groups.

As noted in the present application, Applicants have discovered that novel monomer-dimer mixtures, wherein the dimer (of Formula II) has at least one primary carboxamide

substituent (and in various embodiments may have two primary carboxamide substituents, as currently recited in claim 1) and the monomer (of Formula I) does not contain any primary carboxamide substituents, have unexpectedly and favorably lower osmolality and viscosity values than would be predicted based solely upon the contribution of the monomer and dimer in the mixture. More notably, Applicants have surprisingly found that compositions arising from such monomer-dimer mixtures had favorable intermolecular attractions (between the dimers of Formula II and the monomers of Formula I). This appears to result in intermolecular aggregation, thereby reducing the effective number of particles present in the solution and hence the osmolality of the mixture, as well. (See, e.g., para. [0025].)

**(ii) Felder**

Felder generally discloses an injectable aqueous formulation containing radiopaque contrast agents useful for X-ray imaging of a human or animal body. (See, e.g., the Abstract.) More particularly, Felder discloses injectable aqueous solutions comprise mixtures of non-ionic and water-soluble iodinated aromatic compounds, preferably constituted by: (a) compounds comprising an aromatic nucleus which is at least triiodo-substituted; and, (b) compounds comprising at least two aromatic nuclei variably bound together, each one at least triiodo-substituted. (See, e.g., col. 1, lns. 15-22.) Felder further discloses two alternative or different ways to decrease osmolality. The first is by keeping the total iodine content of aqueous solutions between a desired range, which favors molecular aggregation.[1] The second is to increase the number of atoms of iodine per molecule by covalently binding together two or more triiodonated aromatic nuclei through suitable alkylenic bridges, functionally substituted or not, to obtain the oligomeric structures, thus reducing the number of particles in solution. (See, e.g., col. 2, lns. 30-37.) It is through the second approach (i.e., reducing the number of particles in the solution) that Felder attempts to lower osmolality. Finally, Felder discloses that ioversol can be used as the monomer in the oligomeric mixture.

As recognized by the Office, Felder fails to disclose or suggest combining ioversol with a dimer that falls within Formula II of pending claim 1 (e.g., such as iosmin). Recognizing this deficiency, the Office combines Felder with Sovak in an attempt to render the subject matter of Applicants' claim 1 obvious.

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1 Aggregation is known in the art and generally refers to the tendency of large molecules to combine in clusters or clumps. (See, e.g., Hawley's Condensed Chemical Dictionary, 13th Edition, page 26.)

### (iii) Sovak

Sovak discloses triiodo-5-aminoisophthaldiamides that provide low viscosity and low osmolality. (See, e.g., the Abstract.) The compositions can be used as non-ionic radiographic contrast media. Sovak discloses that iosmin (or iosimenol) can be used as a dimeric compound in the compositions.

## B. The Claimed Subject Matter is not Obvious

The Office argues that it would have been obvious to one of ordinary skill in the art to incorporate the dimers (e.g., iosmin) as disclosed by Sovak into the composition disclosed by Felder, because Sovak teaches that the dimers of Applicants' Formula II are stable in aqueous solutions, readily form supersaturated solutions which remain stable, have good biological tolerance and have a high iodine content. (See, e.g., pages 5-6 of the present Office action.) Applicants respectfully disagree.

Applicants submit that one of ordinary skill in the art would lack motivation to combine the monomers of Felder with the dimers of Sovak in order to arrive at the composition required in Applicants' claim 1, which unexpectedly has a favorably lower osmolality. As noted above, Applicants recognize an objective of Felder is to use a mixture comprising a monomer and dimer to decrease the osmolality of a composition. However, in order to achieve this goal, Felder opts to reduce the number of particles in solution (i.e., solvated particles). One of ordinary skill in the art would readily understand this to be the case, in view of the dimers disclosed in Table 3 of Felder. Notably, the "A" groups disclosed therein are all large and sterically shield the adjacent iodine moieties. Furthermore, these large "A" groups contain at least 2 hydroxyl (OH) groups, which increase hydrophilicity and thereby aid with water solubility.

In contrast, it is clear that Sovak attempts to reduce the osmolality of the compositions disclosed therein by aggregation. Specifically, Applicants note that one of ordinary skill in the art would readily understand that the dimers disclosed in Sovak use primary carboxamide groups, which are small and which do not sterically shield the adjacent iodine moieties, thus producing hydrophobic regions in the contrast media molecules. As such, one of ordinary skill in the art would further understand that the dimers in Sovak (as well as those recited in Applicants' claim 1) affect osmolality by means of aggregation, rather than by means of a

reduction in the number of solvated particles (as in Felder).

In view of the foregoing, it is to be noted that Felder and Sovak utilize distinctly different mechanism to affect osmolality. As such, Applicants submit that one having ordinary skill in the art would clearly lack the motivation to combine the teachings of these references. In fact, Applicants submit that one of ordinary skill in the art would actually be taught away from such a combination, because of the belief that the inclusion of the molecules disclosed by Sovak in a solution in which dimers affect osmolality through aggregation (as in Felder) would actually disrupt the aggregation and lead to an increase in osmolality. Specifically, it is to be noted that the monomers of Formula I in Applicants' claim 1 do not include primary carboxamide moieties (i.e., $-CONH_2$ moieties), and thus do not contain exposed iodine moieties or the hydrophobic regions related thereto. As a result, one having ordinary skill in the art would have thought that the monomers detailed in claim 1 would actually disrupt aggregation of the dimers, thus having a detrimental effect on osmolality (i.e., increasing osmolality).

Applicants further submit that it would not have been obvious to use the dimers of Sovak in the composition of Felder because, given the teachings of these references, one of ordinary skill in the art would have expected the osmolality of the composition to actually be higher than the theoretical value, as a result of disruption to dimer aggregation. In contrast to what one of ordinary skill in the art would have expected here, it is to be noted that the compositions in claim 1 actually show an osmolality similar to the theoretical osmolality (see, e.g., Table 2 in the published application). Thus, Applicants submit it is a surprising result that the compositions of claim 1 do not increase the osmolality above the theoretical value, and that this result would not have been expected to occur by one of ordinary skill in the art.

In view of the foregoing, Applicants respectfully submit that the subject matter of claim 1, as well as all claims depending therefrom, are patentable over the combination of Felder and Sovak. Reconsideration of these rejections is therefore requested.

## CONCLUSION

In view of the foregoing, Applicant respectfully requests reconsideration and allowance of all pending claims.

Applicant hereby authorizes the Commissioner to charge Deposit Account No. 01-2384 for any fees due in connection with the submission of this Amendment A, including a one (1) month extension of time.

Respectfully submitted,

/Derick E. Allen/

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VIA EFS